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REVIEW

Exercise oscillatory ventilation: Mechanisms and prognostic significance

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Abstract

Alteration in breathing patterns characterized by cyclic variation of ventilation during rest and during exercise has been recognized in patients with advanced heart failure (HF) for nearly two centuries. Periodic breathing (PB) during exercise is known as exercise oscillatory ventilation (EOV) and is characterized by the periods of hyperpnea and hypopnea without interposed apnea. EOV is a non-invasive parameter detected during submaximal cardiopulmonary exercise testing. Presence of EOV during exercise in HF patients indicates significant impairment in resting and exercise hemodynamic parameters. EOV is also an independent risk factor for poor prognosis in HF patients both with reduced and preserved ejection fraction irrespective of other gas exchange variables. Circulatory delay, increased chemosensitivity, pulmonary congestion and increased ergoreflex signaling have been proposed as the mechanisms underlying the generation of EOV in HF patients. There is no proven treatment of EOV but its reversal has been noted with phosphodiesterase inhibitors, exercise training and acetazolamide in relatively small studies. In this review, we discuss the mechanistic basis of PB during exercise and the clinical implications of recognizing PB patterns in patients with HF.

Key words: Exercise; Oscillatory ventilation; Heart failure

Core tip: Alteration in breathing patterns in patients with advanced heart failure (HF) characterized by cyclic variation of ventilation with a period of approximately one minute is known as periodic breathing. Periodic breathing during exercise, known as exercise oscillatory ventilation (EOV), is an oscillatory ventilatory pattern during

exercise that persists for at least 60% of the exercise test with an amplitude ≥ 15% of the average resting value. Circulatory delay, pulmonary congestion and chemoreceptor sensitivity has been proposed to cause generation of EOV. EOV is found to be an independent predictor of worse outcome irrespective of other gas exchange variables in HF patients.

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INTRODUCTION

Impaired cardiac filling or ejection of the blood are the cardinal features of heart failure (HF) which leads to multiple organ systems dysfunctions[1] with dyspnea on exertion and exercise intolerance being the most common. Alteration in breathing patterns with cyclic variation of breathing secondary to instability in respiratory control has been a recognized feature of HF for almost two centuries[2,3]. Cheyne[2] (1818) first described a severe form of disordered breathing during rest characterized by alternating hyperpnea and hypopnea with intervals of apnea lasting almost a minute in a patient with HF and similar case was described by Stokes[3] nearly three decades later (1854) after which the condition was named Cheyne-Stokes breathing.

Periodic breathing (PB) characterized by cyclic variation of ventilation with or without interposed apnea have been observed at rest[4], during sleep[4-7] and during exercise[8-10] (Figure 1) in HF patients. Sleep disordered breathing such as obstructive sleep apnea (OSA) and central sleep apnea (CSA) has been observed in nearly 50% of stable HF patients[6] with CSA being significantly more prevalent (40%) than OSA. In one study, the presence of sleep disordered breathing at night was accurately predicted by concomitant daytime PB (AUC 0.821, $P < 0.01$ at receiver operating characteristic analysis, sensitivity 75%, specificity 75%)[4].

An unusual crescendo-decrescendo ventilatory response to exercise in patients with heart disease without resting Cheyne-Stokes breathing was initially reported by Weber[11] and further described by Kremser *et al*[12] in 1987. This phenomenon of periodic oscillatory breathing during exertion without interposed apnea is now known as exercise PB or exercise oscillatory ventilation (EOV) (Figure 2). EOV has recently been recognized in significant percentage of symptomatic HF patients, both with reduced[4,9,10,12-17] and preserved[18] left ventricular ejection fraction (LVEF). Despite the frequent occurrence of PB in patients with HF, pathophysiologic mechanisms that induce irregular breathing as well as the therapeutic modalities to reverse this condition in HF still remain incompletely understood. In this review, we focus specifically on EOV discerned in the context of measuring expired gas exchange variables during exercise through cardiopulmonary exercise testing.

CARDIOPULMONARY EXERCISE TESTING AND EOV

Cardiopulmonary exercise testing (CPET) provides a unique opportunity to evaluate patient's aerobic capacity with breath-by-breath expired gas parameters[19]. Besides providing information about patient's functional capacity with peak oxygen uptake (VO_2)[20], CPET is also helpful in delineating pulmonary vascular abnormalities in HF patients. Studies have shown that ventilatory efficiency (V_E/VCO_2 slope)[21,22] is even better predictor of HF outcomes than peak VO_2. EOV on the other hand is discerned in HF patients during submaximal exercise which makes it a very attractive CPET parameter in those patients who are not able to complete maximal effort exercise testing.

EOV

Definitions

Presence of EOV during CPET is identified by ventilatory oscillations with a typical cycle length and amplitude but there are a lot of variations on its definition[23]. Cycle length of an oscillation in V_E is the time between nadirs of two ventilatory oscillations and the amplitude of oscillation is the difference between the peak V_E during an oscillation and the nadirs in V_E (Figure 2)[24]. Some of the definitions used for EOV are: (1) Kremser *et al*[12] and Corrà *et al*[10,13]: Oscillations in V_E with a cycle length of approximately 1 min, amplitude > 15% of resting V_E, and duration > 60% (> 66%[12]) of exercise duration; (2) Ben-Dov *et al*[25]: 3 or more consecutive regular oscillations in V_E with oscillation amplitude > 25% of average V_E and cycle length 30-60 s; (3) Leite *et al*[15]: Three or more cycles of regular oscillation in V_E with standard deviation of 3 consecutive cycle lengths within 20% of the average and minimal average amplitude of oscillation > 5 L/min; and (4) Sun *et al*[24]: Three or more consecutive cyclic fluctuations in V_E, amplitude > 30% of concurrent mean V_E, oscillation of ≥ 3 gas exchange variables, cycle length of 40-140 s.

The American Heart Association consensus statement has defined EOV as an oscillatory ventilatory pattern that persists for at least 60% of the exercise test at amplitude 15% or more of the average resting value[19]. Due to the lack of automated measurement methods, presence of EOV during CPET is usually analyzed manually which may have lead to variations in its definitions and appropriate identification. More recently custom software has been used to identify EOV during exercise[26,27].

Prevalence of EOV

The prevalence of EOV has been different based on

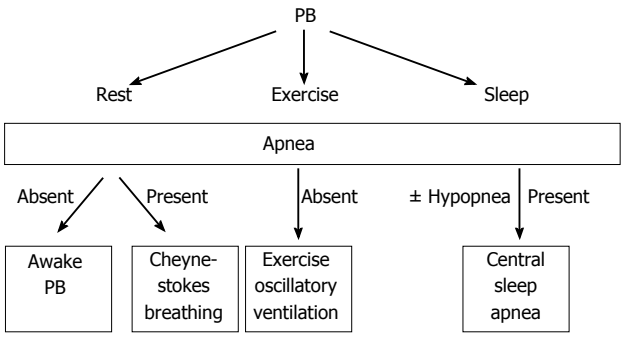

Figure 1 Types of periodic breathing in heart failure patients. PB: Periodic breathing.

the severity and type of HF patient population studied. Patients with HF with reduced ejection fraction (HFrEF) has been found to have EOV prevalence of 12%-58% [8-10,12,13,15,16,18,24,28]. We found EOV prevalence of 45% in a subset of patients with HFrEF (n = 56, mean ± SD: LVEF = 30% ± 6%, peak VO_2 = 12.4 ± 0.5 mL/kg per minute)[8]. EOV is similarly common in patients with HF and preserved ejection fraction (HFpEF)[18,29-31] with one previous study reported prevalence of 31%[18]. Olson *et al*[29] found that 41% of HF patients with EOV had LVEF ≥ 40%, and in the study by Matsuki *et al*[30] the mean LVEF in HF patients with EOV was 41.3 ± 16.3.

Mechanisms of generation of EOV

There is limited data regarding the mechanistic basis for EOV despite its significant association with poor outcomes in HF patients[32]. The control of the normal ventilation is through the feedback loop between pulmonary gas exchanging capillaries and peripheral chemoreceptors located in the carotid bodies and the central chemoreceptors located in the medulla (Figure 3)[33-37]. Any instability of this ventilatory regulation can lead to generation of oscillatory respiratory pattern. The generation of crescendo and decrescendo respiratory pattern can be caused by: (1) Circulatory delay (*i.e.,* increased circulation time from the lung to the brain and chemoreceptors due to reduced cardiac index leading to delay in information transfer)[15,36,37]; (2) increase in controller gain (*i.e.,* increased central and peripheral chemoreceptor sensitivity to $PaCO_2$ and PaO_2)[14,35,38]; or (3) reduction in system damping (*i.e.,* baroreflex impairment) (Figure 3). The possible mechanisms responsible for generation of PB during exercise (*i.e.,* EOV) have largely been extrapolated from studies of PB at rest[39] and during sleep[15,40] even though there has been limited overlap between PB during exercise and during sleep[13].

Circulatory delay: Reduced cardiac output in patients with HF increases the circulation time from lungs to chemoreceptors and respiratory centers. This delayed transfer of information has been postulated to generate late feedback signals leading to oscillations in ventilation[41]. Hypotension and circulatory delay has been shown to induce cardiorespiratory oscillations in experimental rat models[42]. Similarly reduced resting CI and prolonged lung-to ear circulation time (LECT) were the major determinants of PB at rest in HF patients in one previous study[43]. LVEF has also been noted to be significantly lower in HF with PB compared to those without PB[44]. Delayed generation of respiratory and pulmonary blood flow oscillations during exercise compared to LVEF fluctuations in HF patients also supports delayed circulation causing alterations in respiratory feedback mechanisms[45].

In a study of 56 HFrEF patients, those with EOV demonstrated a greater degree of hemodynamic impairment both at rest and during exercise and had 25% lower cumulative CI compared to HF patients without EOV[8]. The amplitude and duration of oscillations were inversely related to exercise CI, and the changes in cycle length and amplitude of EOV after 12 wk of treatment with sildenafil were inversely related to changes in CI[8]. In another small study (n = 17, age 68 ± 12 years), patients with advanced HF, as reflected by a lower peak VO_2 and higher V_E/VCO_2 slope, had a longer cycle length of ventilatory oscillations and a longer phase difference between oscillating VO_2 and V_E[46]. Attenuation of EOV during high-intensity exercise could be due to increased CI during exercise leading to reduced circulation time which supports circulatory delay as an important determining factor for the generation of EOV. However, some investigators have argued against contribution of circulatory delay to EOV but did not directly measure cardiac output or circulation time[45].

Increased chemosensitivity: Increased carotid and aortic chemoreceptor sensitivity to minimal changes in arterial O_2 and CO_2 may contribute to sympathetic overactivity which leads to excessive and irregular ventilation during exercise[47]. Enhanced hypoxic and central hypercapneic chemosensitivity may cause increased ventilatory response (V_E/VCO_2) to exercise in HF patients[48]. Such chronically increased ventilation causes reduction in arterial concentration of both CO_2 and bicarbonate[49] which weakens the blood's ability to buffer against changes in CO_2 levels leading to overly sensitive ventilatory control system. Pitt *et al*[50] in 1907 observed that a modest increase in partial pressure of CO_2 triggers a cycle of hyperventilation-induced reduction in $PaCO_2$ until the apnea threshold is reached leading to Cheyne-Stokes breathing. In a quantitative algebraic analysis of the dynamic cardiorespiratory physiology, circulatory delay and increased chemoreflex gain were found to be the primary factors causing EOV[47]. In both experimental cat models and stable HF patients, inhalation of 100% O_2 decreased the peripheral chemoreceptor discharge and thus oscillatory ventilation[34,42]. Steens *et al*[51] noticed that inhalation of 3% CO_2 virtually eradicated Cheyne Stokes Respiration in HFrEF patients with stable NYHA class Ⅲ-Ⅳ symptoms. Similarly dihydrocodeine attenuated PB by reducing chemosensitivity in 42% of HF patients[34].

Despite the proposed mechanism of increased peripheral chemoreceptor sensitivity causing EOV, there may be other non-peripheral chemoreceptor mediated

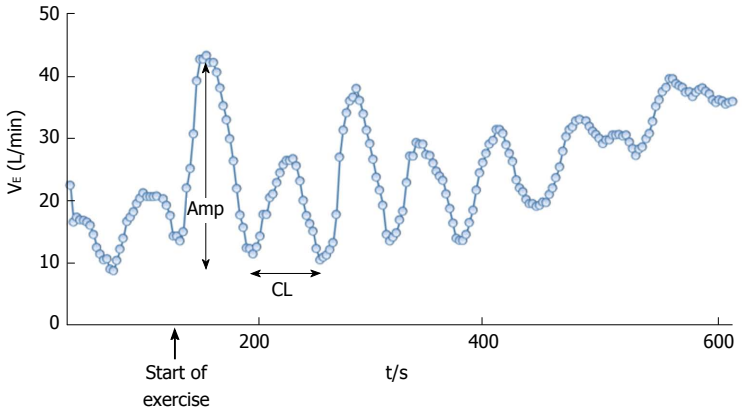

Figure 2 Oscillatory ventilation during exercise. CL: Cycle length; Amp: Amplitude of oscillation; V_E: Ventilation.

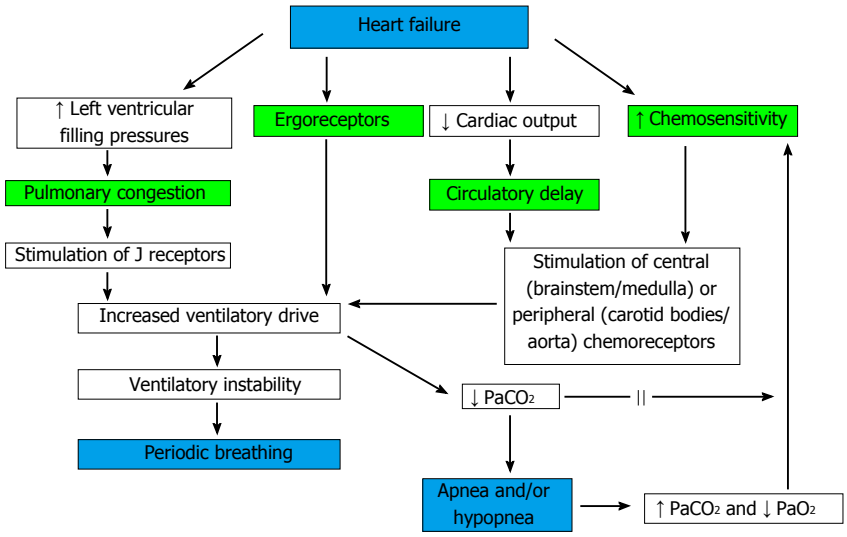

Figure 3 Mechanisms of generation of periodic breathing in heart failure patients.

mechanisms involved in mediating increased ventilatory response to exercise[52]. In one study of HFrEF patients, arterial blood gases ($PaCO_2$ and PaO_2) at rest and average values across the first 6 min of exercise in HF patients had no relationship with EOV[8]. The amplitude and duration of EOV was also not related to mean $PaCO_2$ which argues against a $PaCO_2$ set point close to the apnea threshold, serving as a major determinant of the presence of EOV in HF patients[8].

Pulmonary congestion: Pulmonary congestion[53] and decreased lung compliance[54] has been postulated to cause overstimulation of the ventilatory control center which leads to hyperventilation and decrease in PCO_2[55] and thus generating PB. Elevated pulmonary capillary wedge pressure, a surrogate marker for pulmonary congestion, stretches pulmonary C fibers (J receptors)[56] which in turn stimulates the medullary respiratory center *via* vagal afferents[57], leading to rapid shallow breathing, hypocapnia, and initiation of PB at rest. The damping effects of O_2 and CO_2 stores which prevent oscillations are also reduced by pulmonary congestion and a small fluctuation in CO_2 level makes the respiratory control unstable in HF patients with pulmonary congestion[37]. In 1943, Christie *et al*[58] were able to induce PB due to pulmonary congestion by occluding a pulmonary vein. Recent findings of increased resting and exercise cardiac filling pressures[8,30] and higher NT-proBNP[30] levels in HF patients with EOV compared to those without EOV extends their findings. Despite these findings suggestive of role of pulmonary congestion as the etiology for EOV, this mechanism has been questioned by some investigators[45] which noticed disappearance of EOV during later exercise in HF patients despite an increase in PCWP.

Ergoreflex signaling: HF causes metabolic and structural abnormalities in the skeletal muscles which may also lead to enhanced ergoreflex signaling during exercise which has been postulated as an etiologic factor for generation of PB. Increased ergoreflex may be associated with worse NYHA class, decreased exercise tolerance, and hyperventilation during exercise in HF patients[59-61]. In a study by Pardaens *et al*[62], ergoreflex

activity contributed to hyperventilation in HF patients with a history of recent decompensation or persistent symptoms. Oscillations in output of neurologic stimuli from the medullary vasomotor center may explain disappearance of respiratory oscillations found at rest or at low levels of exercise during more intense exercise[43]. Decreased activation of both CO_2 chemoreflex and the ergoreflex has recently been shown to decrease ventilatory drive after cardiac resynchronization therapy[63]. Despite the proposed contribution of ergoreceptors to the autonomic, hemodynamic, and respiratory responses to exercise in HF patients, further investigation is needed to establish its relationship to hyperventilation and EOV in HF patients.

Prognostic Significance of EOV

It has been well known that the prevalence of EOV tracks with the metrics of HF severity such as higher NYHA class, lower peak VO_2, higher V_E/VCO_2 slopes and lower $PETCO_2$[8,12,13,15,16,24,28-30,64-69] (Table 1). EOV actually provides strong independent prognostic information regarding the severity of HF even after adjustment for these variables. The initial study describing the prognostic significance of PB by Ponikowski *et al*[34] predicted poor 2-year survival in HF patients with abnormal breathing patterns which was independent of peak VO_2 and NYHA class. Similarly Bard *et al*[17] also observed resting ventilatory variation to be the best predictor of mortality in 44 matched HFrEF patients. Leite *et al*[15] and Corrà *et al*[10,13] both found that HF patients with EOV had 3-fold higher mortality compared to those without EOV (Table 1). When EOV is present along with other abnormal ventilatory patterns either during sleep or during exercise, the risk of mortality increases even further as those observed by Corrà *et al*[13] in a group of HF patients who had abnormal breathing patterns during sleep and EOV during exercise (54% adverse events in patients with EOV and apnea hypopnea index > 30/h *vs* 17% with EOV alone, OR = 6.65, 95%CI: 2.6-17.1, $P < 0.01$). Similarly the odds of dying in 6 mo increased by 4-fold (9.4 to 38.9) when EOV was present along with elevated V_E/VCO_2 slope in another group of HF patients[24]. EOV is not only known to be the independent predictor of overall mortality and sudden cardiac death in HFrEF patients but also the strongest predictor of mortality in HFpEF patients in multivariate models[9]. Ingle *et al*[28] observed EOV to be the predictor of mortality independent of peak VO_2, V_E/VCO_2 slope, LVEF, age, and 6-min walking distance. EOV has recently been recognized as a potent prognostic indicator in patients with congenital heart disease as EOV along with the percentage of maximum predicted HR were independent predictors of the combined outcome of death, transplantation or cardiovascular hospitalization in patients who underwent Fontan procedure[27].

The superior prognostic value of EOV and V_E/VCO_2 slope compared to peak VO_2 has been observed in multiple studies examining the relative predictive values of various CPET variables (Table 1). EOV along with other CPET derived variables (V_E/VCO_2 slope, oxygen uptake efficiency slope and ventilatory equivalent for CO_2 nadir) has been shown to outperform the traditional Heart Failure Survival Score in predicting outcomes in patients with mild-to-moderate HF[70]. Guazzi *et al*[71] recently characterized EOV in patients with broader cardiovascular risk factors and found the EOV to be an indicator of worse CV risk factor profile in patients even without clinical manifestations of HF. The feasibility of EOV measurements during submaximal exercise during CPET makes it particularly attractive in HF population who are unable to do maximum effort exercise testing.

EOV reversibility

Various pharmacological or surgical interventions has been performed in HF patients to identify the potential reversibility of EOV but there has not been any large scale clinical trial with EOV as the primary endpoint. In a small randomized double-blind placebo controlled trial of HFrEF patients, serial assessment of EOV before and after 12 wk of sildenafil treatment showed reduction in EOV cycle length and oscillatory amplitude and increase in exercise CI in the sildenafil group compared to placebo[8]. The changes in oscillatory cycle length and amplitude after sildenafil treatment were inversely related to changes in exercise CI[8]. This finding was further supported by another study from Guazzi *et al*[18] who noted resolution of EOV in the majority of patients treated with sildenafil, although EOV was not a pre-specified endpoint in these trials with small number of study subjects ($n < 40$).

Attenuation of PB has been observed with valvular[72] and open heart surgeries, and cardiac transplantation[73]. There are few other studies involving small number of patients that showed resolution of EOV with different therapeutic interventions. For example, Ribeiro *et al*[74] noticed reduction in EOV with phosphodiesterase-3 inhibitor milrinone in three patients and Castro *et al*[75] reported reversal of EOV and improvement in NYHA class with exercise training in one HF patient despite no change in LVEF. Reversal of EOV in 71% of stable HFrEF patients has also been observed after 3 mo of outpatient exercise training program[76]. This highlights the importance of exercise therapy in both HFrEF and HFpEF patients. Recent studies have shown that inhalation of CO_2[77] and acetazolamide[77,78] treatment significantly reduced PB during exercise in HF patients. Kazimierczak *et al*[67] noticed reversal of EOV in more than 85% of the HF patients after three months of nocturnal adaptive servoventilation even though it was a very small study ($n = 8$). Finally, in an experimental study of pacing induced-CHF rabbit models, carotid body chemoreceptor denervation reduced disordered breathing patterns[79].

CLINICAL IMPLICATIONS

EOV is a significant prognostic indicator of adverse outcomes in HF patients. EOV identification at submaximal levels of exercise during CPET and the possibility of EOV reversal with HF interventions makes it a potential

Table 1 Prevalence and clinical significance of exercise oscillatory ventilation in heart failure patients

Ref.	No. of patients	NYHA class, LVEF	Prevalence of PB	Clinical and prognostic significance of EOV	Significant mortality predictors
Corrà *et al*[10], (2002)	323	NYHA 2.2 ± 0.9 LVEF 24 ± 8	12%	EOV present in 28% of nonsurvivors *vs* 9% survivors, follow-up period 22 ± 11 mo	NYHA class, LVEF, peak VO_2
Leite *et al*[15], (2003)	84	NYHA 2-4 LVEF 35 ± 7	30%	EOV independently increased the risk of death by 2.97 fold, median follow-up period of 11.3 mo	Peak VO_2, NYHA class, V_E/VCO_2 slope
Corrà *et al*[13], (2006)	133	NYHA 2.3 ± 0.7 LVEF 23 ± 7	21%	42% mortality in EOV patients *vs* 15% in non EOV, follow-up period 39 ± 11 mo	NYHA class, peak VO_2, V_E/VCO_2 slope, AHI, LVEF, lower rate of beta blocker use, peak HR
Guazzi *et al*[9], (2007)	156	NYHA 1-4 LVEF 35 ± 11	33%	EOV was the strongest predictor of overall and SCD mortality. EOV present in 100% arrhythmic and 47% nonarrhythmic deaths, follow-up period 28 ± 25 mo	LV mass, LVESV. V_E/VCO_2 slope maintained a predictive value as to overall cardiac mortality and pump failure death outperforming EOV as predictor of pump failure mortality
Guazzi *et al*[18], (2008)	556 (405 HFrEF, 151 HFpEF)	NYHA 2.4 ± 0.8 in HFrEF, 2.0 ± 0.9 in HFpEF	35% in HFrEF, 31% in HFpEF	EOV was strongest predictor of mortality in HFpEF compared to HFrEF in multivariate models; EOV was similar predictor of mortality in both HFrEF and HFpEF without LVAD or transplant	V_E/VCO_2 slope in multivariate model, peak VO_2 in univariate model
Arena *et al*[16], (2008)	154	NYHA 2.2 LVEF 30 ± 14	36%	Event (death, transplant or LVAD) free survival 55% in EOV *vs* 82% in non EOV patients, follow-up period 3 yr	V_E/VCO_2 slope, LVEF
Bard *et al*[17], (2008)	44	LVEF 19 ± 7	13%	Death or transplant rate 68% in patients with PB *vs* 52% without PB	Resting ventilatory variation more powerful predictor of mortality than peak VO_2 and V_E/VCO_2 slope
Olson *et al*[29], (2008)	47	NYHA 2.6 ± 0.8 LVEF 37 ± 17	7%	EOV associated with higher V_E/VCO_2 slope, V_D/V_T, lower $PETCO_2$, higher NYHA class	
Ingle *et al*[28], (2009)	240	LVEF 34 ± 6	31% by Leite and 25% by Corrá Criteria	50% of patients diagnosed with EOV by Corrá criteria and 58% diagnosed by Leite criteria died within 1 yr	
Sun *et al*[24], (2010)	580	NYHA 2-4 LVEF 26 ± 7	51%	EOV combined with elevated V_E/VCO_2 (≥ 155% predicted) resulted in an OR of 39 for 6 mo mortality	Peak VO_2, AT, peak oxygen pulse significantly worse in nonsurvivors
Ueshima *et al*[68], (2010)	50	NYHA 1-3	28%	EOV associated with lower peak VO_2 and higher V_D/V_T	
Murphy *et al*[8], (2011)	56	NYHA 2-4 LVEF 30 ± 6	45%	EOV related to ↓exercise cardiac output and ↑cardiac filling pressures	
Scardovi *et al*[31], (2012)	370	NYHA 1-3 LVEF 41% (range 34%-50%)	58%	EOV, V_E/VCO_2 slope and its ratio to peak VO_2 predicted all-cause mortality independent of LVEF	Hemoglobin level, creatinine, BMI, HF admissions in the previous year
Matsuki *et al*[30], 2013	46	NYHA 3 LVEF 41 ± 16	44%	EOV patients had ↑cardiac filling pressures, higher NT-proBNP value, ↑V_E/VCO_2 slope, low $PETCO_2$ and greater Borg dyspnea score	
Nathan *et al*[27], (2015)	253	NYHA 1-3	38%	5 yr rate of death or transplant 14.1% in Fontan patients with EOV *vs* 4.1% of those without EOV	NYHA class, peak HR

LVEF and follow-up periods are in mean ± SD. NYHA: New York Heart Association; VO_2: Oxygen uptake; V_E: Ventilator efficiency; AHI: Apnea-hyponea index; AT: Anaerobic threshold; HR: Heart rate; LVEF: Left ventricular ejection fraction; HFrEF: HF and reduced ejection fraction; HFpEF: HF and preserved ejection fraction; HF: Heart failure; OR: Odds ratio; SCD: Sudden cardiac death; LVAD: Left ventricular assist device; LVESV: Left ventricular end systolic volume; $PETCO_2$: End tidal partial pressure of carbon dioxide; V_D/V_T: Ratio of physiologic dead space over tidal volume; BMI: Body mass index; NT-proBNP: N terminal pro brain natriuretic peptide.

surrogate end point of interest for HF clinical trials focused on improvement in gas exchange variables and exercise hemodynamics. There is still a need for HF studies with specific EOV endpoint to identify whether HF interventions such as diuretic therapy, exercise training, phosphodiesterase inhibitors, cardiac resynchronization therapy, intensification of neurohormonal blockade, cardiac surgery or other emerging therapies such as neprilysin inhibitors will successfully attenuate EOV, and if that modification translates into improvement in underlying cardiac dysfunction and clinical outcome of HF patients.

CONCLUSION

EOV is a noninvasive and reproducible exercise parameter which is easily recognizable during submaximal cardiopulmonary exercise testing. EOV has been proven to be a strong predictor of reduced survival in HF patients irrespective of the echocardiographic and gas exchange

variables. Presence of EOV in a HF patient indicates significant impairment in resting and exercise cardiac hemodynamic parameters, especially when the cycle length of EOV is longer than one minute and when EOV occurs early during exercise. HF patients presenting with EOV may therefore need an intensification of therapy to optimize cardiac hemodynamics, and improve overall symptoms and functional capacity.

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